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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/502,041	11/07/2005	Gary Levy	9579-90	1924

1059 7590 01/04/2008

BERESKIN AND PARR
40 KING STREET WEST
BOX 401
TORONTO, ON M5H 3Y2
CANADA

EXAMINER	
SZPERKA, MICHAEL EDWARD	
ART UNIT	**PAPER NUMBER**
1644	

MAIL DATE	DELIVERY MODE
01/04/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/502,041	LEVY ET AL.	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *2,4,9-11 and 14-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5-8,12 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/29/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: Sequence Alignment

DETAILED ACTION

1. Please note that the examiner of record for your application has changed. To aid in paper matching, please address all future correspondence to Michael Szperka, Art Unit 1644, Technology Center 1600.

Applicant's response received October 30, 2007 is acknowledged.

Claims 1-19 are pending in the instant application.

Applicant's election of Group I, claims 1, 3, 5-8, 12, and 13, drawn to methods of inhibiting immune responses to porcine fgl2 as part of transplanting porcine organs by administering antibodies that bind porcine fgl2 in the reply filed on October 30, 2007 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 2, 4, 9-11, and 14-19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on October 30, 2007 as explained above.

Claims 1, 3, 5-8, 12, and 13 are under examination as they read on methods of administering anti-porcine fgl2 antibodies to inhibit immune responses in tissue transplantation settings.

Information Disclosure Statement

2. Applicant's IDS form received 7/29/04 is acknowledged and has been considered.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claim 1, 5-8, 12, and 13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of inhibiting an immune response by administering antibodies that bind fgl2 in an organ transplantation setting, does not reasonably provide enablement for more. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant has claimed broad methods of administering "agents" that inhibit or suppress immune responses by inhibiting porcine fgl2 as well as methods of modulating immune responses by administering fgl2 "modulators". The specification discloses that antibodies which bind fgl2 inhibit its activity and thus can be used in methods of inhibiting graft rejection. However, the breadth of the term "agent" is not limited to antibodies but also encompasses nucleic acids, proteins, peptides, peptide mimetics, carbohydrates and small molecule organic and inorganic compounds as per page 18 of the instant specification. Note that "agent" and "modulator" appear to be synonymous, save for the fact that the "agents" of claim 1 are inhibitory whereas no such functional limitation is placed on the "modulators" of claim 7. The specification does not appear to disclose working examples concerning the breadth of "agents", and even if one could screen for molecules that inhibited the activity of fgl2, the starting points and structures for many of the agents, such as the small molecules that would be put through such a screening process, are not disclosed. Further, the nature of the "activity" that is to be inhibited is not clear. While the specification discloses that fgl2 is a prothrombinase that appears to comprise enzymatic activity that can directly cleave prothrombin to thrombin (thus initiating blood clotting), "agents" do not necessarily comprise the ability to inhibit enzymatic activity. Indeed, page 18 makes clear that agents can inhibit the expression

or activity of fgl2, while line 10 of page 4 of the instant specification and Marazzi et al. disclose that the constitutive function of fgl2 is not known. Since activity does not appear to be limited to the enzymatic ability to cleave thrombin, what "activity" would a skilled artisan use as the readout in a screening assay? Note that "modulators" can increase or increase expression and/or activity of fgl2 and as such compound the question of what is to be used as a readout in a screening assay.

Claim 7 recites "modulating" an immune response in an animal in need thereof, but it is unclear what animals need treatment given that "modulation" encompasses both increasing and decreasing fgl2 expression/activity (whatever "activity" may mean). Given that the claimed method is performed on an animal, and that methods are not performed just for fun, the method must have some therapeutic or diagnostic utility. What therapeutic or diagnostic use is being addressed in claim 7 is completely unclear, especially given that it can either increase or decrease fgl2 expression and/or activity. Indeed, the specification indicates that it is desirable to inhibit fgl2 in tissue transplantation settings to limit graft rejection (see also claim 1), yet claim 8 encompasses administering "modulators" which would increase fgl2 expression/activity and thus make the graft more likely to be rejected. It is not clear that any animal would ever be in need of having a transplanted organ rejected. Further, claim 13 recites that the "modulator" is an antibody, but the specification does not appear to disclose that antibodies comprise the properties of increasing the expression/activity of fgl2.

Therefore, given the breadth of the claims, the guidance and direction in the specification and working examples, and the teachings of the art, a skilled artisan would be unable to practice the full breadth of applicant's claimed methods without conducting additional unpredictable research.

5. Claims 1, 5-8, 12, and 13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicant has claimed broad methods of administering "agents" and "modulators" that alter the expression and/or activity of fgl2. The structure of such agents and modulators are disclosed on page 18 as encompassing nucleic acids, proteins, peptides, peptide mimetics, carbohydrates, and small molecule organic and inorganic compounds. The specification discloses that fgl2 comprises enzymatic activity to cleave prothrombin to thrombin, but "fgl2 activity" is not defined as being solely limited to its function as a prothrombinase. "Activities" of fgl2 in addition to being a prothrombinase do not appear to be disclosed. Note that the "agents" administered in the instant claims are required to inhibit fgl2 whereas no such functional limitation is placed upon the genus of administered "modulators", and that "inhibition" and occur by either decreasing expression of fgl2 or by decreasing the "activity" of fgl2 (whatever that may mean).

The guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, § 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species, then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, January 5, 2001, see especially page 1106 column 3).

In University of California v. Eli Lilly and Co. (CAFC) 43 USPQ2d 1398, the court noted: "A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene (in the instant case, a peptide) does, rather than what it is. See Fiers, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes (peptides) may achieve that result. The description requirement of the patent statute requires a description of an

invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin [e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material."

The court has also noted that "Adequate written description requires a precise definition, such as by structure, formula, chemical name or physical properties, not a mere wish or plan for obtaining the claimed chemical invention." Id. at 1566, 43 USPQ2d at 1404 (quoting Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606). Also see Enzo-Biochem v. Gen-Probe 01-1230 (CAFC 2002).

Based upon the disclosure of the specification concerning what molecules are considered to be part of the genus of "agents" it is clear that there is no common, conserved, core structure among nucleic acids, peptides, carbohydrates and small molecules that give rise to their functional property of inhibiting fgl2. "Modulators" are even less defined since the same structures give rise to the diametrically opposed functional properties of inhibiting and stimulating fgl2. Note also that the specification does not disclose working examples covering the breadth of the genus of molecules encompassed by the terms "agent" and "modulator" and that the disclosure of specific species, such as antibodies, are not representative because of the aforementioned structural differences between antibodies, nucleic acids, carbohydrates, etc...

Therefore, it appears that the broad genus of "agents" and "modulators" recited in the instant method claims lack adequate written description because there is no disclosed correlation between structure and function, especially in view of the lack of a specifically defined function. As such a skilled artisan would reasonably conclude that applicant was not in possession of the recited genus of "agents" and "modulators" at the time the application was filed.

6. Claim 6 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claim 6, as currently amended to depend from claim 1, recites a method wherein an agent that inhibits porcine fgl2 is administered to suppress an immune response to a tissue or organ obtained from a pig deficient in fgl2 expression. While the specification discloses administration of organs from transgenic pigs lacking fgl2, and discloses administering agents, such as antibodies, to inhibit porcine fgl2, the specification does not appear to teach the simultaneous use of agents and transgenic organs. Further, it does not make logical sense that a skilled artisan would administer an agent to inhibit a porcine molecule when said porcine molecule is not present. In response to this office action, applicant can either point out where in the specification specific support for simultaneous use is disclosed or cancel the new matter. It should be noted that claim 6 was originally an independent claim which did not recite administering of "agents" that inhibit fgl2.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

8. Claims 1, 3, 5, 7, 8, 12, and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Levy et al. (WO 98/51335, of record on the 7/29/04 IDS).

Levy et al. disclose methods of inhibiting the activity or expression of fgl2 to treat transplantation rejection (see entire document, particularly the abstract and lines 27-31 of page 2). One disclosed method for inhibiting fgl2 activity is to administer antibodies which bind fgl2 for the treatment of the immune coagulation response which occurs as part of allograft and xenograft rejections (ibid and lines 3 and 4 of page 1). The antibodies used can be polyclonal or monoclonal, and a preferred epitope is disclosed (DRYPSGNCGLYYSSG) that is 100% conserved between human and murine fgl-2 sequences (see particularly from line 25 of page 6 to line 7 of page 9 and Figure 5). Such antibodies are disclosed for use in organ transplantation, and working examples are provided demonstrating the efficacy of such antibodies when transplanting organs between different strains of rats and between rats and guinea pigs (allografts and xenografts respectively, see particularly lines 34-37 of page 6 and Example 2). They further disclose that anti-fgl2 antibodies can be used for porcine to primate xenotransplantations. As such, Levy et al. disclose administering anti-fgl2 antibodies to treat graft rejection when transplanting pig organs. Note that the specifically disclosed epitope is also completely conserved in porcine fgl2 as evidenced by the enclosed sequence alignment. Thus, human, mouse, and pig fgl2 all comprise the antibody binding epitope disclose by Levy et al. and therefore the epitope is a fragment of SEQ ID NO:2 of the instant specification. Also note that the human and mouse sequences disclosed by Levy et al. are homologs of SEQ ID NO:2.

Therefore, the prior art anticipates the claimed invention.

9. Claims 1, 3, 5, 7, 8, 12, and 13 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent 6,805,863.

The disclosure of the '863 patent is identical to that of Levy et al. discussed above, differing only in pagination and formatting. As such, the claims are rejected as

being anticipated by the '863 patent for the same reasons discussed for the anticipation of the instant claims by the disclosure of Levy et al.

Therefore, the prior art anticipates the claimed invention.

Double Patenting

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 1, 3, 5, 7, 8, 12, and 13 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 6,805,863 in view of WO 98/51335.

The claims of the '863 patent recite administering an antibody that binds a specific epitope of fgl2 to treat graft rejection and differ from the instant claimed invention in that they do not recite that the grafted organ is of porcine origin

The '335 document (which is a WIPO publication identical to the specification of the '863 patent) discloses that antibodies that bind fgl2 are to be used in

xenotransplantation methods, such transferring porcine organs to primates. The '35 document discloses that the epitope recited in the claims of the '863 patent is completely conserved between the evolutionarily widely separated species of human and mice, and provide working examples wherein such antibodies were used to successfully used in inhibiting xenograft rejections.

Therefore, a person of ordinary skill in the art would have been motivated at the time the invention was made to modify the administration methods of the '863 patent to include porcine organs since the '335 document discloses the use of anti-fgl2 antibodies in transplants involving pig organs and would have a reasonable expectation of success in doing so based upon the conservation of the epitope recognized by the antibody among evolutionarily distant animals and its disclosed working examples of xenotransplantation.

Claim Objections

12. Claims 5 and 12 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claims, or amend the claims to place the claims in proper dependent form, or rewrite the claims in independent form.

Specifically, the independent claims recite "porcine fgl2" yet dependent claims 5 and 12 recite specific SEQ ID numbers as well as analogs, homologs, and fragments of said SEQ ID numbers. It is not reasonable that a fragment of a protein is the protein itself. Homologs read on fgl2 from other animal species such as humans and mice, which negates the limitation "porcine fgl2". Similarly, the specification defines analogs as comprising mutations including substitutions, insertions, truncations and non-naturally occurring amino acids such that the sequence could never be found naturally occurring in any pig, thus making it unreasonable to call the analog a "porcine fgl2". As such, these recitations appear to broaden the scope of the claims from which they depend.

13. No claims are allowable.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is 571-272-2934. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Michael Szperka, Ph.D.
Patent Examiner
Art Unit 1644
December 20, 2007